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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/555,735	11/30/2006	Lawrence M. Blatt	INTM-019/01US 095185-2162	2009

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EXAMINER	
HOWARD, ZACHARY C	

ART UNIT	PAPER NUMBER
1646	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/555,735	BLATT, LAWRENCE M.	
	Examiner	Art Unit	
	ZACHARY C. HOWARD	1646	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-20* is/are pending in the application.

4a) Of the above claim(s) *3,4 and 6-20* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2 and 5* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-20* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *07 November 2005* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *6/14/07*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Status of Application, Amendments and/or Claims

Claims 1-20 are pending in the instant application.

Election/Restrictions

Applicant's election of Group I, claims 1-5, in the reply filed on 5/14/08 is acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 6-20 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Applicant's election of the species of SEQ ID NO: 15 in the reply filed on 5/14/08 is acknowledged.

Claims 3 and 4 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected species, there being no allowable generic or linking claim.

Claims 1, 2 and 5 are under consideration, as they read upon the elected species of SEQ ID NO: 15.

Priority

The instant application claims priority to Provisional Application 60/471,404, filed 5/16/2003. The '404 application does not appear to include the sequence of SEQ ID NO: 15. Therefore, the earliest date to which SEQ ID NO: 15 merits priority is 5/13/04, which is the filing date of PCT/US04/15357 (of which the instant application is a 371 of).

Application Data Sheet

Applicants submitted an ADS on 11/30/06 that includes "Domestic Priority Information". This information incorrectly lists the filing date of U.S. Provisional

Application 60/471404 as May 13th, 2003. USPTO records indicate that this application was filed on May 16th, 2003. In addition, the first box of the first line of the Domestic Priority Information is blank where the instant Application Number (10/555735) should be present. Appropriate correction is required.

Claim Rejections - 35 USC § 112, 1st paragraph, enablement

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claims contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d 731, 737, 8 USPQ2d 1400, 1404 (Fed. Cir. 1988).

The nature of the invention is synthetic CXCR3 polypeptide ligands. CXCR3 is a chemokine G-protein coupled receptor (G-PCR) and three ligands of this receptor are IP-10 (CXCL10); I-TAC (CXCL11) and Mig (CXCL9). The scope of the claim 1 is as follows. The polypeptide of claim 1 must comprise a polypeptide of from about 70 to about 125 amino acids in length. Because the recitation "comprise" allows for further unrecited elements, this claims encompasses a longer protein encompassing a polypeptide of from about 70 to about 125 amino acids in length. Thus, this limitation is met by any polypeptide of about 70 amino acids or longer. The claims further recites

that "the amino acid sequence of the polypeptide comprising, in sequence, discrete sub-sequences corresponding in amino acid identity and number to sub-sequences of different, naturally occurring CXCR3 ligands selected from IP-10, I-TAC, Mig". The recitation of "different ... ligands" is interpreted broadly as an adjective describing the recited Markush-type group (i.e., this group constitutes three different ligands). Thus, the recitation does not clearly limit the synthetic ligand to containing sequences from two or three of these ligands, and has been interpreted broadly to encompass any polypeptide comprising at least one "sub-sequence" from IP-10, I-TAC and Mig as well as any hybrid encoding sequences from two or three of these ligands. The recitation of "corresponding in amino acid identity and number" is broadly interpreted to indicate that the "sub-sequence has the same type and number of amino acids as the portion of the natural ligand from which it is derived. Finally, the claim recites that the sequence "differs from the amino acid sequence of naturally occurring CXCR3 ligands IP-10, I-TAC and Mig". This excludes the sequences of IP-10 (SEQ ID NO: 12); I-TAC (SEQ ID NO: 13) and Mig (SEQ ID NO: 14) from the genus encompassed by claim 1. In summary, claim 1 encompasses essentially any mutant comprising a sequence from IP-10, I-TAC or Mig, as well as combinations thereof.

Claim 2 depends from claim 1 and limits the ligand to one of a Markush-type group that includes the elected species SEQ ID NO: 15 under consideration. Figure 3 of the instant application shows SEQ ID NO: 15 (98 amino acids). A comparison with the native IP-10 (SEQ ID NO: 12); I-TAC (SEQ ID NO: 13) and Mig (SEQ ID NO: 14) sequences shows the origin of the following residues of SEQ ID NO: 15: 1-22 (Mig residues 1-22 = signal sequence of Mig); 23-39 (I-TAC residues 23-39); 40-60 (IP-10 residues 40-60); 61-79 (Mig residues 61-79); 80-89 (I-TAC residues 80-89) and 90-98 (IP-10 residues 90-98). Thus, SEQ ID NO: 15 has six "subsequences" including two from each of IP-10, I-TAC and Mig.

Claim 5 depends from claim 1 and is directed to a composition comprising a ligand of any of claims 1-4.

The specification does not provide any working examples with either SEQ ID NO: 15 or any of the other variants encompassed by the claims. The specification teaches

that "whether a subject synthetic CXCR3 ligand functions as a CXCR3 agonist is readily determined using known assays. For example, assays for CXCR3 agonist activity are discussed in U.S. Patent No. 6,184,358 and U.S. Pat. No. 6,491,906" (¶ 53 on page 12). The specification does not actually teach whether or not SEQ ID NO: 15 has any activity similar to IP-10, I-TAC and Mig, such as binding to the CXCR3 receptor. The specification suggests that the ligands can be used to treat liver fibrosis (page 38-46); cancer (page 46-51); angiogenic disorders (page 51-53) and bacterial infections (page 53-55), but the specification does not teach any working examples of treatment of such diseases with SEQ ID NO: 15 or any other ligand encompassed by the claims. Furthermore, the specification does not provide any teachings regarding portions of IP-10, I-TAC and Mig that are critical for activity.

The problem of predicting protein structure from sequence data and in turn utilizing predicted structural determinations to ascertain functional aspects of the protein is extremely complex. While it is known that many amino acid substitutions are generally possible in any given protein, the positions within the protein's sequence where such amino acid substitutions can be made with a reasonable expectation of success are limited. Certain positions in the sequence are critical to the protein's structure/function relationship, e.g. such as various sites or regions directly involved in binding, activity and in providing the correct three-dimensional spatial orientation of binding and active sites. Particular regions may also be critical determinants of antigenicity. These regions can tolerate only relatively conservative substitutions or no substitutions [see Wells (18 September 1990) "Additivity of Mutational Effects in Proteins." Biochemistry **29**(37): 8509-8517; Ngo *et al.* (2 March 1995) "The Protein Folding Problem and Tertiary Structure Prediction, Chapter 14: Computational Complexity Protein Structure Prediction, and the Levinthal Paradox" pp. 492-495]. However, Applicants have provided little or no guidance beyond the mere presentation of sequence data to enable one of ordinary skill in the art to determine, without undue experimentation, the positions in the protein which are tolerant to change, and the nature and extent of changes that can be made in these positions.

Although the specification outlines art-recognized procedures for producing variants, this is not adequate guidance as to the nature of active variants that may be constructed, but is merely an invitation to the artisan to use the current invention as a starting point for further experimentation. Even if an active or binding site were identified in the specification, it may not be sufficient, as the ordinary artisan would immediately recognize that an active or binding site must assume the proper three-dimensional configuration to be active, which conformation is dependent upon surrounding residues; therefore substitution of non-essential residues can often destroy activity. The art recognizes that function cannot be predicted from structure alone [Bork (2000) "Powers and Pitfalls in Sequence Analysis: The 70% Hurdle." Genome Research **10**:398-400; Skolnick and Fetrow (2000) "From gene to protein structure and function: novel applications of computational approaches in the genomic era." Trends in Biotech. **18**(1): 34-39; Doerks *et al.* (June 1998) "Protein annotation: detective work for function prediction." Trends in Genetics **14**(6): 248-250; Smith and Zhang (November 1997) "The challenges of genome sequence annotation or 'The devil is in the details'." Nature Biotechnology **15**:1222-1223; Brenner (April 1999) "Errors in genome annotation." Trends in Genetics **15**(4): 132-133; Bork and Bairoch (October 1996) "Go hunting in sequence databases but watch out for the traps." Trends in Genetics **12**(10): 425-427].

Furthermore, it is unpredictable whether or not the changes present in one protein (IP-10, I-TAC or Mig) sequence can be used to make similar changes in one of the other sequences and retain functionality. The situation is analogous to that of orthologous proteins found in different animal species. As noted above, single amino acid changes can drastically affect protein functionality if occurring in a critical residue; thus, making a change to one protein based a related sequence may require additional compensatory changes elsewhere in the sequence. As noted in Ferrer-Costa (2007. J Mol Biol. 365: 249-256), non-human sequences may contain residues that are disease-associated in humans, but which are not disease-associated in the non-human animal: these changes are explained by compensatory changes elsewhere in the protein (see Abstract).

Due to the large quantity of experimentation necessary to generate the large number of variants recited in the claims and possibly screen same for activity, the lack of direction/guidance presented in the specification regarding which structural features are required in order to provide activity, the absence of working examples directed to same, the complex nature of the invention, the state of the prior art which establishes the unpredictability of the effects of mutation on protein structure and function, and the breadth of the claims which fail to recite any structural or functional limitations, undue experimentation would be required of the skilled artisan to make and/or use the claimed invention in its full scope.

Claim Rejections - 35 USC § 112, 1st paragraph, written description

Claims 1, 2 and 5 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In making a determination of whether the application complies with the written description requirement of 35 U.S.C. 112, first paragraph, it is necessary to understand what Applicants are claiming and what Applicants have possession of.

Claims 1 and 5 are genus claims because the claim is directed to variant polypeptides. The scope of these claims are discussed above in the rejection for lack of enablement. Claim 2 is also a genus claim that is limited to SEQ ID NO: 15-20, of which SEQ ID NO: 15 is the elected species under consideration.

Claims 1, 2 and 5 all require that the polypeptide is a "CXCR3 polypeptide ligand". In order to be a ligand of the CXCR3 receptor, the polypeptide must be able to bind to CXCR3. Thus, the recitation of "CXCR3 polypeptide ligand" is a functional limitation that requires CXCR3 binding. However, the instant specification fails to describe any particular variant of IP-10, I-TAC and Mig that can bind to CXCR3. The instant specification further fails to describe whether or not SEQ ID NO: 15 retains the ability to bind to CXCR3.

The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant identifying characteristics, i.e. structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between structure and function, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. In the instant case, the specification fails to provide sufficient descriptive information, such as definitive structural or functional features, or critical conserved regions, of the genus of polypeptides, or of the functionality of SEQ ID NO: 15. There is not even identification of any particular portion of the structure that must be conserved. Structural features that could distinguish encoded polypeptides in the genus from others in the protein class are missing from the disclosure. The specification and claims do not provide any description of what changes should be made. There is no description of the sites at which variability may be tolerated and there is no information regarding the relation of structure to function. The general knowledge and level of skill in the art do not supplement the omitted description because specific, not general, guidance is what is needed. Furthermore, the prior art does not provide compensatory structural or correlative teachings sufficient to enable one of skill to isolate and identify the polypeptides encompassed. Thus, no identifying characteristics or properties of the instant polypeptides are provided such that one of skill would be able to predictably identify the encompassed molecules as being identical to those instantly claimed. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus. One of skill in the art would reasonably conclude that the disclosure fails to provide a representative number of species to describe the genus. Thus, Applicants were not in possession of the claimed genus.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, whatever is now claimed" (pg 1117). The specification does

not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed" (pg 1116). As discussed above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of polypeptides, and therefore conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the method of isolation. Adequate written description requires more than a mere statement that it is part of the invention and reference to a potential method of isolating it. The compound itself is required. See *Fiers v. Revel*, 25 USPQ2d 1601 at 1606 (CAFC 1993) and *Amgen Inc. v. Chugai Pharmaceutical Co. Ltd.*, 18 USPQ2d 1016. One cannot describe what one has not conceived. See *Fiddes v. Baird*, 30 USPQ2d 1481 at 1483. In Fiddes, claims directed to mammalian FGFs were found to be unpatentable due to lack of written description for that broad class. The specification provided only the bovine sequence.

Therefore, claims 1, 2 and 5 fail to meet the written description provision of 35 U.S.C. §112, first paragraph. Applicant is reminded that *Vas-Cath* makes clear that the written description provision of 35 U.S.C. §112 is severable from its enablement provision (pg 1115).

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1 and 5 are rejected under 35 U.S.C. 102(b) as being anticipated by Barone, May 5-10, 2002. ARVO Annual Meeting Abstract Search and Program Planner, 1 page.

Barone teaches a "fusion product of Mig and IP-10" that is 214 amino acids length. Such a fusion protein meets all of the limitations of claim 1 as follows. The Mig:IP-10 fusion is a "synthetic CXCR3 polypeptide ligand" because Mig and IP-10 are each CXCR3 ligands. The Mig:IP-10 fusion protein is 214 amino acids in length, which means that it "comprises a polypeptide of from about 70 to about 125 amino acids in

length" (any protein about 70 amino acids in length would comprise a polypeptide within said range). The Mig:IP-10 fusion protein amino acid sequence comprises discrete sub-sequences (from Mig and IP-10) of different, naturally occurring ligands selected from IP-10, I-TAC and Mig (the phrase "selected from IP-10, I-TAC, and Mig" is interpreted broadly as a Markush-type group where the selected sequences can be from IP-10, I-TAC and/or Mig). The Mig:IP-10 fusion protein differs from the amino acid sequence of each of IP-10, I-TAC and Mig. Thus, the teachings of Barone anticipate claim 1.

Barone further teaches "lentiviral supernatants containing the Mig:IP-10 fusion product". This supernatant meets the limitations of claim 5, which encompasses a composition comprising the synthetic CXCR3 ligand of claim 1.

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1 and 5 are rejected under 35 U.S.C. 102(a) as being anticipated by Clark-Lewis et al. Journal of Biological Chemistry. 278(1): 289-295; published in JBC Papers in Press on November 1, 2002. The earliest filing date to which the instant application claims priority is May 16, 2003.

Clark-Lewis teaches I-TAC/IP10 hybrid proteins (Figure 4, see I-TAC-H1, -H2 and -H3). Each is between 70 and 80 amino acids in length and includes sequences from I-TAC and IP10. Such a fusion protein meets all of the limitations of claim 1 as follows. The I-TAC/IP10 hybrid proteins are a "synthetic CXCR3 polypeptide ligand" because I-TAC and IP-10 are each CXCR3 ligands. The I-TAC/IP10 hybrid proteins are between 70 and 80 amino acids in length, which means each "comprises a polypeptide of from about 70 to about 125 amino acids in length" (any protein about 70 amino acids in length would comprise a polypeptide within said range). The I-TAC/IP10 hybrid proteins amino acid sequences comprises discrete sub-sequences (from I-TAC and IP-10) of different, naturally occurring ligands selected from IP-10, I-TAC and Mig (the phrase "selected from IP-10, I-TAC, and Mig" is interpreted broadly as a Markush-type group where the selected sequences can be from IP-10, I-TAC and/or Mig). The I-

TAC/IP10 hybrid proteins differ from the amino acid sequence of each of IP-10, I-TAC and Mig. Thus, the teachings of Clark-Lewis anticipate claim 1.

Clark-Lewis further teaches incubation of the I-TAC/IP10 hybrid proteins with cells for receptor binding assays (Figure 5). As taught on page 290, the receptor binding assays were performed in RPMI 640 medium. This composition meets the limitations of claim 5, which encompasses a composition comprising the synthetic CXCR3 ligand of claim 1.

Note

No prior art has been found that teaches a ligand comprising the amino acid sequence as set forth in SEQ ID NO: 15.

Conclusion

No claims are allowable.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Zachary C. Howard whose telephone number is 571-272-2877. The examiner can normally be reached on M-F 9:30 AM - 6:00 PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary B. Nickol can be reached on 571-272-0835. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/Z. C. H./
Examiner, Art Unit 1646

/Gary B. Nickol /
Supervisory Patent Examiner, Art Unit 1646